Remarks

Claim 18 is pending. Claim 26 has been canceled. Support for the amendment to claim 18 can be found on page 12, lines 9-10 of the application as filed.

In item 4 of the Office Action dated 9th August 2005, the Examiner has rejected claim 18 under 35 U.S.C. 112 for failing to comply with the written description requirement. However, the Examiner has helpfully pointed out that, on page 12 of the specification, there is support for "the treatment of peripheral sensory neuropathy by nerve regeneration". Therefore, claim 18 has been amended to reflect this wording.

The Examiner also rejected claim 26 under 35 U.S.C. 112 on the basis that "the claim limitation does not appear in the specification in the context where the written description is made concerning the use of a galanin agonist in the treatment of peripheral sensory neuropathy wherein said treatment is by nerve regeneration". In order to meet the Examiner's concerns, claim 26 has been canceled without prejudice. However, for the avoidance of doubt, the Applicant wishes to place on the record that the cancellation of claim 26 is in no way to be taken as an indication that the term "subject", as recited in claim 18, is to be construed as not encompassing human subjects. The skilled person would clearly understand that this term includes human subjects. In addition, there is reference throughout the specification to several conditions which would only routinely be treated in human subjects, for example, diabetes mellitus (page 2), Alzheimer's Disease (page 2) and idiopathic small stature and anorexia (both on page 13). This gives the skilled person further reason to conclude that the term "subject" includes human subjects.

The Examiner further rejected claim 18 under 35 U.S.C. 112 because the specification does not disclose details of specific galanin agonists which may be used in the claimed method. The Examiner has indicated that the relationship between function and structure of a molecule is poorly understood and cited a chapter by Rudinger, in a textbook edited by J.A. Parsons and published in 1976. The Applicant respectfully traverses this rejection and offers the following arguments in response. Firstly, the cited document was published twenty years prior to the priority date of the current application and before the identification of galanin. During that time, the fields of biochemistry, neuroscience and pharmacology had changed a great deal and had substantially advanced in skill and understanding. Secondly, a person of ordinary skill in the art would have been able, at the priority date (24th July 1996) of the patent application, to identify galanin agonists without undue experimentation. At the priority date at least six galanin agonists (in addition to the native full-length neuropeptide) had been identified. These include a number of chimeric ligands (where the N-terminal portion of galanin is fused to another peptide), including M15 [GAL-(1-13)-substance P-(5-11)amide], M35 [galanin-(1-13)-bradykinin-(2-9)-amide], M40 [galanin[1- 13]-Pro-Pro-[Ala-Leu]2-Ala amide], and Gal(1-14)-[Abu8]SCY-I.

The following studies, using a variety of paradigms, demonstrated that each of the above ligands acts as a galanin agonist. M15 and M35 act as galanin agonists by causing contraction of jejunal muscle strips and relaxing dispersed smooth muscle cells from the rat small bowel (Gu *et al.* (1993) J. Pharmacol. Exp. Ther. **266** 912-918). Similarly, M15 acts as a galanin agonist by causing contraction of longitudinal muscle strips of the human colon in vitro (Katsoulis *et al.* (1996) Scand. J. Gastroenterol. **31** 446-451). Further, M15 and Gal(1-14)-[Abu8]SCY-I, acting

as galanin agonists, both evoked concentration-dependent contractions of gastric smooth muscle strips (Korolkiewicz *et al.* (1996) Pharmacol. Res. **33** 361-365).

In insulin-producing RIN m5F cells, M15 and M35 both produce a biphasic response in calcium levels identical to galanin, demonstrating that both chimeric peptides act in this system as galanin agonists (Fridolf & Ahren (1993) Biochem. Biophys. Res. Commun. **191** 1224-1229; Kask *et al.* (1995) Regul. Pept. **59** 341-348). Similarly, a later study showed that M40 acts as a galanin agonist by stimulating glucose-induced insulin release from isolated mouse pancreatic islets (Bartfai *et al.* (1993) Proc. Natl. Acad. Sci. U.S.A. **90** 11287-11291). M40 also acts as a galanin agonist in the spinal cord (Xu *et al.* (1995) Br. J. Pharmacol. **116** 2076-2080). In addition, two N-terminally extended forms of galanin, galanin-(-7-29) and galanin-(-9-29) had also been shown to have agonistic properties on spinal flexor reflex excitability in decerebrate, spinalized, unanaesthetized rats (Bedecs *et al.* (1994) Eur. J. Pharmacol. **259** 151-6).

Other assays to determine if a compound is a galanin agonist include the technique described by Botella *et al.* (1995) in the journal Gastroenterology **108** 3-11, in which they showed that galanin is an agonist at two types of receptor in intestinal smooth muscle where it contracts or relaxes the tissue. Another way of identifying whether or not a compound was a galanin agonist would have been to examine its effects on the cholinergic control of vasculature tone in the anaesthetized rat, as reported by Barblivien *et al.* (1995) in the journal Neuroreport **6** 1849-1852. In this respect the agonist effect of galanin is to inhibit the vasodilatory cholinergic input.

It can been seen from the above studies that a variety of assays have been described which would allow a person of ordinary skill in the art to readily determine whether a compound

is a galanin agonist and is, therefore, suitable for use in the method according to claim 18 of the patent application.

In light of the reasons given above, the Examiner is requested to withdraw the §112 rejection of claim 18.

Claim 18 has also been rejected under 35 U.S.C. 103(a) as being unpatentable over Luo *et al.* ("Luo") in view of Zhang *et al.* ("Zhang"). The Examiner asserts that "It would have been obvious to one of ordinary skill in the art at the time the invention was made to use galanin as a treatment following peripheral nerve damage as taught by Luo in primates, including humans, as taught by Zhang, for therapeutic purposes, including the treatment of peripheral nerve damage and pain resulting from such." The Applicant respectfully traverses this rejection and offers the following arguments in response.

It seems that the Examiner considers that a compound which is effective in the amelioration of neuropathic pain that occurs as a result of nerve injury (as taught by Luo in rats and then hypothesized by Zhang in primates) would have been obvious to the skilled person as having an effective use in the treatment of nerve damage by nerve regeneration.

The Examiner is respectfully reminded that, at the priority date of the application, there were a large number of drugs available for the treatment of chronic neuropathic pain which had, nor have, no known effects on stimulating or improving nerve regeneration. Examples include morphine and other opioids; aspirin; non-steroidal anti-inflammatory agents (NSAIDs); antidepressants such as Amitriptyline or Imipramine; and anti-epileptics such as Tegretol. There is common clinical experience that, when drug treatment with these agents for various pain

conditions is halted or discontinued, the pain rapidly returns, arguing against any regeneration leading to restoration of the function of the damaged nerve.

Further, studies have shown that:-

Morphine inhibits facial nerve regeneration (Sinatra, R. S. and Ford, D. H. (1979) Brain Res. **175** 315-25);

The antidepressant Imipramine has no effect on peripheral nerve regeneration *in vivo* (De Medinaceli L. *et al.* (1986) Exp. Neurology **94** 788-90).

Therefore, Applicant respectfully disagrees with the Examiner's statement that "it would be obvious... to use galanin as a treatment for nerve damage". There is nothing in the existing literature to make one of ordinary skill in the art think that chronic treatment of neuropathic pain (arising from nerve injury or damage), irrespective of the cause or the drug used, would promote nerve regeneration. Indeed, there was some data at the priority date of the current application to allow the opposite hypothesis to be proposed. Subsequent publications have supported this, for example Sabouni, F., *et al.* (Biochem. Biophys. Res. Commun. (1998) **248** 165-7) which reported that aspirin delays nerve outgrowth from cultured DRG neurons.

All of the existing data at the priority date of the current application was focused on treating pain and not on stimulating nerve regeneration. These two fundamental patho-physiological processes are very different and most, if not all, of the anti-pain drugs listed above act at the level of the spinal cord and brain to reduce electrical and chemical excitability and thus reduce pain transmission. In contrast, drugs that stimulate nerve regeneration do so at the level of the dorsal root ganglion (DRG) and/or the site of nerve injury. As argued in previously filed submissions, the galanin administered by Luo could not have reached the DRG or the site of

injury in the time frame of the experiment and thus could not have affected regeneration. In relation to this, the Applicant notes the Examiner's acknowledgement that "Luo does not teach that his method involves nerve regeneration..."

The Examiner has previously argued (for example, in the Office Action dated 28th January 2004) that the meaning of the word "treatment", as recited in claim 18, is "the act or manner of treating" and not (as proposed by the Applicant) "to effect a cure". In light of this, the Examiner has argued that the inherent properties of galanin to promote nerve regeneration would have the result that, in the experiments of Luo and Zhang, regeneration would have occurred, even though such regeneration was not measured and disclosed. The Applicant has several comments in relation to this.

First, the Examiner is reminded of the requirements for an inherency rejection, as found in section 2112 of the MPEP: "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)". The Examiner has provided no technical reasoning to reasonably support the determination that galanin was used as a treatment following peripheral nerve damage in either Luo *et al.* or Zhang *et al.*

Second, even if an inherent result of galanin use was to promote nerve regeneration, the skilled person was given no incentive from either Luo or Zhang to think that this would be the case. As acknowledged by the Examiner, Luo does not disclose nerve regeneration. Indeed, as previously submitted and supported by the Declaration of Professor Zigmond under 37 C.F.R. §1.132, such nerve regeneration could not possibly have taken place during the time period of the experiments reported in Luo. Zhang shows that the number of galanin positive cells strongly increased in the DRG after transection of the sciatic nerve in monkeys, similar to earlier results obtained in rats, demonstrating that expression of galanin is upregulated following nerve injury. Galanin was, therefore, hypothesized to be a naturally occurring antinociceptive agent, although no pain measurements were taken. At no stage was exogenous galanin or a galanin agonist administered to the animals used in the Zhang experiments. Even if galanin had been administered intrathecally to the animals in the Zhang experiments, as was the case in the animals in the Luo experiments, it would have to gain access to the DRG before regeneration could possibly occur, as previously submitted and as supported by Professor Zigmond's Declaration. Therefore, it is not a necessary feature of the embodiments described in Zhang that nerve regeneration will occur if galanin or a galanin agonist were administered in a method of treatment of peripheral sensory neuropathy, as recited in claim 18 of the current application.

It is difficult to see how the teaching of Luo and Zhang would have made it obvious to the skilled person to invent the new and different use for a galanin agonist in a method for the treatment of peripheral sensory neuropathy in a subject, the method comprising the step of administering a galanin agonist to the subject, as required by claim 18 of the application. The claimed characteristic does not flow from the teachings of Luo and Zhang, since nerve

regeneration could not have occurred in Luo and, in Zhang, galanin is only present in endogenously expressed form inside the DRG and was not exogenously administered.

In addition, the prior art disclosures did not involve the use of a galanin agonist in a method for the treatment of peripheral sensory neuropathy in a subject. The experiments of Luo were not a method for the treatment of peripheral sensory neuropathy and Zhang did not involve the use of a galanin agonist (or galanin itself) in such a treatment and so the subject matter of claim 18 cannot be inherent in these prior art references.

Further to this point, the Applicant respectfully submits that the Examiner's interpretation of the term "treatment" goes against the accepted use of this term in patents which have previously been granted by the USPTO. Many patents have the claim structure "A method of treating [a disease] in a subject comprising the step of administering [a compound known to be effective for some other purpose]". For example, US 6,943,185 includes the claim:

"1. A method of treating cancer in a patient in need thereof, which comprises administering an effective amount of 2-methyl-thiazolidine-2,4-dicarboxylic acid (2-MTDC) and/or one or more of its physiologically tolerable salts to said patient."

2-MTDC is acknowledged in the specification to be known and to have a known use as a hepaprotective agent. The patent indicates that "Nothing was known as yet about the favorable influence of 2-methyl-thiazolidine-2,4-dicarboxylic acid (2-MTDC) and its physiologically tolerable salts on cancer prevention and treatment..." However, despite the inherent property of 2-MTDC being an anti-cancer agent, even where administered for the different use as a hepaprotective agent, the claim has been granted.

Similarly, US 6,927,223 includes the claim:

"5. A method for the treatment of melanoma in a mammal, which method comprises administering to said mammal an effective anti-melanoma amount of a serotonin agent selected from the group consisting of fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram, and pharmaceutically acceptable salts thereof."

The recited compounds are antidepressant compounds, in common use (e.g. fluoextine is sold under the trade mark Prozac™). Apparently, the patentee of US 6,927,223 has found that these compounds also have the inherent property of being effective anti-melanoma agents. Despite these inherent properties of compounds which must almost certainly have been administered to melanoma sufferers for the purpose of treating depression, the claim has been granted.

In both cases, claims have been granted on the basis that "treatment" does not mean "the act or manner of treating" but "to effect a cure". Such claims are commonly used to provide protection to the patentee who has determined that a known compound, having known uses, is also effective in some other area. Even though the steps the practitioner would go through in administering the above compounds ("the act or manner of treating") would be identical when the compound is used for a new use as when it was used for its old use, the claims are granted because the claimed administration aims "to effect a cure" of a certain condition.

In light of the various arguments above, the Applicant respectfully submits that the skilled person would have been given no reason, from reading Luo and Zhang, to contemplate a

method for the treatment of peripheral sensory neuropathy in a subject in need of such treatment, the method comprising the step of administering to the subject an amount of a galanin agonist effective to treat peripheral sensory neuropathy, wherein said peripheral sensory neuropathy is treated by nerve regeneration, as required by claim 18 of this application. There is no discussion in either document (or indeed, in any other document before the priority date of the current application) of the possibility of galanin being a pro-regeneration factor. The Applicant points the Examiner to the fact that, at the top of the second column of page 373 of Zhang, such a pro-regenerative role is hypothesized for another neuropeptide, VIP. Therefore, if Zhang had contemplated such a role for galanin, it would surely have been mentioned here. In fact, no such role is suggested for galanin in either document and, in addition, no data is provided which would have supported such a hypothesis, had it been made. The galanin in Zhang was endogenously expressed and so the skilled person is not pointed to any inherent property of an exogenously administered galanin agonist. Therefore, the method claimed in the current application cannot be considered to have been obvious to the skilled person in view of Luo and Zhang.

The applicant therefore requests removal of this basis for rejection and allowance of claim 18 to issue.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No additional fees are believed due. However, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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